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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,855	07/03/2003	Si-Hyoung Lee	DE-1490	4750

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,855	LEE ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *10-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Election/Restrictions

Applicants' election of Group I (claims 1-9) made on 7/19/2005 is acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants election of the species Tn7 as the transposon; the species of the library as random and enzymes as the target is also acknowledged. Applicants traverse the species restriction (not the groups of invention) in that the species are not patentably distinct. For example the transposon as recited in claim 4 are obvious variants in that they are transposon having remission cites (sites) from a restriction enzyme at both ends thereof. Any transposon is interchangeably used for the transposon in the present invention insofar as they have recognition sites for a restriction enzyme at both ends. Likewise the sub-group B are obvious variants since any random or specific nucleotide sequence consisting of three nucleotides can be used as substituted nucleotides in the method of the invention. The same arguments are applied to the target.

In view of applicants' admission that each of the species in each of the subgroups is obvious variant of one another, the

restriction with respect to the species is withdrawn. Since a prior art found for one species of e.g., transposon would render obvious the other species.

Claims 10-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. The election made on 7/19/2005 was made **without** traverse.

Status of Claims

Claims 1-26 are pending

Claims 10-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-9 are under examination.

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicants' cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Drawings

The drawings are objected to because there is no Seq. ID. Nos. assigned for the sequences in the drawing Figures e.g.,

Fig. 1. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A representative number of species

means that the species, which are adequately described, are representative of the entire genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure indicates that the applicants have invented species sufficient to constitute the gen[us]. Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

The specification provides a written description of the specific enzyme, chitosanase gene as the target gene modified by three specific nucleotides at the defined position of the gene to produce a mutant library of the chitosanase gene. Other than this specific enzyme, no other target gene has been described. Neither do any other transposon and its derivatives or multiple three nucleotides randomly substituted at any target site other than does specifically described has also been completely disclosed. The specification does not show any structural correlation of the single enzyme species, chitosonase, to other enzymes, let alone, to the other huge scope of the structurally unrelated genus target. None of the components in the method has any defined structure. The numerous factors or variables included in the genus are infinite even for a specific component of the claim. Examples of these factors are the structures of any target DNA that can be mutated by multiple substitution of

three nucleotides, the position along the structures where substitution can be done, the length of target DNA i.e., whether the whole or fragment of the DNA is used. The target DNA is only one of the undefined variables of the genus claim. There are still the other undefined variables that also have to be determined and analyzed. For example, the multiple three substituents do not recite the kind of nucleotides that are comprised therein, the type of randomization of the multiple three substituents. Also, the type of transposons, especially its derivatives, which can be inserted and the insertion site and cutting enzymes such that the target DNA would at least retain its function. These are only but a few of the infinite variables covered by the huge scope of the genus claims. In biotechnological invention one cannot necessarily claim a genus after only describing a single species because there may be unforeseeable results obtained from species other than those specifically described. The more unpredictable the art the greater the showing required (e.g. by (representative examples) for both enablement and adequate disclosure. A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from

other materials. University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993). See also University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

Applicants, at the time of filing, are deemed to have not invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). Applicants are further referred to the CAFC decision in the University of California vs. Eli Lilly and Co. CAFC 43 USPQ2d 1398 7/22/1997 with respect to adequate disclosure of the scope of the presently claimed method. Adequate disclosure, like enablement, requires representative examples, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention. See In re Riat (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University of California v. Eli Lilly and Co. (for disclosure).

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the target DNA, transposon, multiple three nucleotide substituents, the randomization of these nucleotides. See further the numerous undefined variables of the genus claim, as defined above.

2). The specification failed to provide working examples for any of the numerous and different types of DNA target,

transposon, random nucleotides, the multiples of three random substituents and screening techniques that can be used in the instant method.

3). The breadth of the claims encompasses a large diversity of mutant DNA target by the random peptide, the predetermination of the sites of variations in a target or the nucleotides involve in the variation. It is well known in the art, that it is often difficult to know where insertions in the gene and its encoded protein for mutations can be done without deleteriously affecting the protein function or its global structure. The diversity of the inserts is not easily estimated. It may be for example, that only a small subset of possible peptide sequences are presented efficiently by a particular expression system. And, it is not always easy to follow the expression of peptides in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert, especially for biological methods.

4). The state of the prior art is such that techniques are specifically applied for a predetermined protein or target.

5). The art is inherently unpredictable because it is not possible to predict which predetermined (variations) of amino acids would result in the desired random mutant with a desired pharmacologic activity. It is generally known that the

conformational freedom that promotes binding, e.g., by modifying the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the protein in ways difficult to predict and measure. Some proteins accommodate insertions (variations) at numerous sites throughout their primary sequence. Others are much less accommodating. It is difficult in general to predict which proteins are robust to insertions, and which sites in a particular protein are best suited to insertion of multiple independent sequences. The complex spatial configuration of amino acid side chains in proteins and the interrelationship of different side chains in the randomized sites are insufficiently understood to allow for such predictions. Selective (site-directed) mutagenesis and saturation mutagenesis are of limited utility for the study of protein structure and function in view of the enormous number of possible variations in complex proteins. There are still no rules that have emerged that allow structure to be related to sequence in any simple fashion (even as applied to the actual compounds).

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous undefined random peptide in a protein would result in a mutations having a desired property without undue experimentation. Applicants do not adequately

enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

The language is so broad that it causes claim to have a potential scope of protection beyond that which is justified by the disclosure. To be entitled to such weight in method claims, the recited structural limitation therein must affect the method in a manipulative sense and not to amount to the mere claiming [of a use] of a generic structure. (Ex parte Pfeiffer, 782 O.G. 639, 135 USPQ 31 (1961).

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is confusing, as the steps therein do not appear to correlate with one another. For example in step 2, it recites deleting the nucleotides originating form the transposon and the

nucleotides of the target DNA duplicated during the insertion of the transposon, at one cut terminus of the target DNA. However, this is confusing, as the transposon inserted in the DNA of the preceding steps has been cut at both ends. The language evolving a polypeptide and a polynucleotide encoding same is unclear as to the meaning of evolving. The preamble is inconsistent with the body of the claims of selecting or screening for the expressed polypeptides. "The expressed-polypeptide" lacks antecedent basis from the preceding steps. It is unclear as to whether the term "multiple" refers to the three nucleotides or a number of three substituents inserted along the target DNA.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayes et al (Cancer Research) in view of Short (20040077090).

Hayes discloses at page 2411 up to page 2413 commencing at Materials and Methods section, a method of pentapeptide scanning mutagenesis technique whereby 5-amino acid insertions are introduced at random in a target protein. It comprises mating in a host E.coli containing a target plasmid and a plasmid, pHT385, a conjugative delivery vector for transposon with a plasmid-free E.Coli recipient strain. Plating the mating mix simultaneously on antibiotics, selecting for the recipient and the target plasmid and transconjugants containing the transposon-target plasmid, cointegrates are isolated. Regenerating the delivery vector and target plasmid into which a copy of the transposon 4430 has been inserted. Tn4430 contains KpnI restriction enzyme sites located 5-bp from both ends of the transposon and duplicates 5-bp of the target site sequence during transposition. By digesting the target palsmid-Tn4430 hybrid with KpnI and religating the digested DNA, the bulk of the transposon is deleted to generate a target plasmid derivative containing a 15-bp insertion. If the insertion is a protein-encoding sequence, this will result in a 5-amino acid insertion in the target protein of target site sequence. Hayes also teaches at page 2415, Discussion section up to page 2416 a site-directed mutagenesis i.e., a single amino acid substitutions on the target site. Hayes does not describe a three-nucleotide substitution in the target site. However, Short

discloses at paragraph [1169] that the use of a degenerate triplet (such as N,N,G/T or an N,N, G/C triplet sequence) is advantageous for several reasons. In one aspect, it provides a means to systematically and fairly easily generates the substitution of the full range of possible amino acids (for a total of 20 amino acids) into each and every amino acid position in a polypeptide. Thus, for a 100 amino acid polypeptide, the instant invention provides a way to systematically and fairly easily generate 2000 distinct species (i.e. 20 possible amino acids per position X 100 amino acid positions). It is appreciated that there is provided, through the use of an oligo containing a degenerate N,N,G/T or an N,N, G/C triplet sequence, 32 individual sequences that code for 20 possible amino acids. Thus, in a reaction vessel in which a parental polynucleotide sequence is subjected to saturation mutagenesis using one such oligo, there are generated 32 distinct progeny polynucleotides encoding 20 distinct polypeptides. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use three nucleotide substitution in the method of Hayes for the advantages taught by Short. These advantages would provide the motivation to one having ordinary skill in the art at the time the invention was made. It would be within the ordinary

skill in the art to pick and choose the number of substitutions as the prior art teaches substitution of one to five amino acids.

Claim 7 is obvious over the disclosure of Short at paragraph [0130] as to the mutagenized molecules including biological molecules. Non-limiting examples of these include antibodies, enzymes, and steroidal and non-steroidal hormones.

Claim 8 is obvious over the disclosure of Short at paragraph [1112] as to the different enzymes encoded by the polynucleotides including, but are not limited to lyases, oxidoreductases, transferases, hydrolases, isomerases and ligases.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
September 5, 2005